Advanced Diagnostic Approaches and Current Medical Management of Insulinomas and Adrenocortical Disease in Ferrets (*Mustela putorius furo*)

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KEYWORDS

• Ferret • Insulinoma • Adrenocortical disease

Large-scale studies documenting the types of neoplasms seen in the domestic ferret (*Mustela putorius furo*) have found that endocrine neoplasms are the most common type reported, with islet cell tumors and adrenocortical tumors making up a large percentage of the neoplasms diagnosed.[1,2] Both of these tumors are commonly seen in middle-aged to older ferrets, although increasing numbers of younger ferrets are being diagnosed. An exception is the black-footed ferret (*Mustela nigripes*), an endangered and genetically distinct species in the United States, that is not plagued by insulinomas and adrenocortical neoplasms despite having a high incidence of neoplastic disease.[3] Although surgical excision is still considered by most practitioners as the treatment of choice for insulinomas and adrenocortical neoplasia, practitioners should be cognizant of the medical therapies available for ferrets when surgery is not an option. This article discusses the proposed causes, current diagnostics, and the medical management of insulinomas and adrenocortical disease.

INSULINOMA

Pancreatic islet beta-cell tumor, more commonly known as insulinoma, is a well-documented neoplasm that produces its effects through the overproduction of insulin.[1,2,4–8] This neoplasm is commonly seen in middle-aged to older ferrets, with a reported incidence of approximately 25% of the neoplasms diagnosed.[1] These

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tumors secrete insulin indiscriminately and are not responsive to inhibitory stimuli such as hypoglycemia and hyperinsulinemia. In addition, rapidly increasing glucose levels, even in the presence of low blood glucose concentration, can stimulate excessive insulin release from these tumors, causing a profound rebound hypoglycemia. Although local tumor recurrence in the pancreas is a common feature, there is a low rate of metastasis to other organs; with the regional lymph nodes, liver, and spleen being the most commonly reported sites.[9,10] In contrast, insulinomas in dogs are usually malignant and have a high rate of gross metastasis at the time of diagnosis.[11] At present, it is thought that there is a genetic cause for the predisposition of insulinomas in ferrets. It has also been theorized that excessive carbohydrate intake may play a role in the development of this disease.[1,4,12] Both sexes are represented, but there are conflicting reports on whether males are slightly overrepresented.[1,8] Most ferrets begin exhibiting clinical signs around 4 years of age, although a functional insulinoma has been reported in a ferret as young as 2 weeks.[2]

Clinical signs include mental dullness, irritability, stargazing, hindlimb weakness, and ataxia. Other common signs noted in ferrets include ptyalism or pawing at the mouth secondary to presumed nausea. Ferrets with severe hypoglycemia may exhibit generalized seizures, which is the most common clinical finding in dogs with insulinomas. The relatively low frequency of generalized seizures in ferrets compared with dogs may be due to the fact that most ferrets are fed ad libitum and have a low-activity lifestyle associated with cage restriction.[11,13] Clinical signs are often episodic, but the severity and frequency of clinical signs often progress if left untreated. Prolonged episodes of severe hypoglycemia can result in neuronal glucose deprivation and cerebral hypoxia, leading to subsequent lesions in the cerebral cortex.[14]

Diagnostics

A presumptive diagnosis of insulinoma is made in ferrets when they demonstrate a fasting blood glucose level lower than 70 mg/dL in the presence of neurologic symptoms that cease after a feeding or intravenous administration of glucose.[8,15] Other causes of hypoglycemia such as sepsis, starvation, hepatic disease, and laboratory artifact should be systematically ruled out. Immediate evaluation of freshly drawn blood with a handheld glucometer provides a quick relative assessment of the blood glucose status. However, most handheld point-of-care glucometers are not validated for ferrets and may report values that are 10 to 20 mg/dL lower than actual glucose levels.[8] If a sample is to be sent to a diagnostic laboratory, immediately centrifuge the collected blood to separate the plasma to minimize artifactual decreases through red cell metabolism. In patients in whom an insulinoma is suspected but the blood glucose is within normal limits (90–125 mg/dL), a carefully monitored 3- to 4-hour fast may be required to confirm hypoglycemia.[8]

Hyperinsulinism can be documented by submitting plasma or serum to laboratories that have validated assays for ferrets. An elevated insulin level with concurrent hypoglycemia is consistent with and supports the diagnosis of an insulinoma. However, normal insulin levels (5–35 μU/mL; 36–251 pmol/L) with concurrent hypoglycemia do not rule out the presence of an insulinoma since there may be erratic production and secretion of insulin by some beta-cell tumors.[8,16,17] Insulin to glucose ratios are no longer recommended because of their high incidence of false positives.[8,17] Studies investigating fructosamine and glycosylated hemoglobin show a direct relationship with serum glucose levels in people and dogs, and studies for their use in ferrets are warranted.[18,19] Nonspecific elevations in alanine aminotransferase and aspartate aminotransferase are sometimes noted and may reflect the presence of hepatic

lipidosis from chronic hypoglycemia.[8] Other changes in blood work are usually unremarkable, and if present may be a result of concurrent disease.

Diagnostic imaging is usually unrewarding, because most insulinomas are only a few millimeters in diameter and may even be microscopic in size. However, rare cases of pancreatic tumors as large as 1 cm in diameter have been observed in the author's practice and could be visualized on ultrasonographic examination. The use of intraoperative ultrasonography of the pancreas has been described in dogs to identify pancreatic nodules, but the result is highly dependent on operator experience.[14,17]

A small clinical study in dogs showed the use of intravenous 1% methylene blue, which is preferentially absorbed by hyperfunctional pancreatic tumors, to enhance visualization of the neoplastic nodules during a laparotomy. Adverse clinical signs in some of the study subjects included pseudocyanosis from damage and lysis of red blood cells.[20] The use of methylene blue has not been investigated in ferrets.

Histologic examination of surgical biopsies is required for definitive diagnosis, and lesions can range from hyperplasia to adenomas to carcinomas, or have a combination of any of these processes. Most insulinomas consist of cords and nests of eosinophilic polyhedral cells on a fine fibrovascular stroma. Although most tumors are usually well encapsulated, some tumors can be infiltrative or unencapsulated (**Fig. 1**). Immunohistochemistry can be used to further characterize pancreatic neoplasms and any metastatic nodules in the surrounding organs. Most pancreatic islet cell tumors express strong immunoreactivity for insulin, although immunostaining for peptide hormones such as glucagon, somatostatin, and pancreatic polypeptide has been occasionally noted. The neuroendocrine markers chromogranin A and neuron-specific enolase are also effective immunocytochemical markers for islet cell tumors in ferrets, and could be used to characterize poorly differentiated pancreatic tumors or metastasis in distant organs that may be insulin negative.[21]

Therapeutics

Management of a hypoglycemic episode

Advise owners on the clinical signs of hypoglycemia and on what measures to take during a hypoglycemic episode. If mild clinical signs such as lethargy or excessive salivation are noted, owners should provide a feed to abate the clinical sign. If

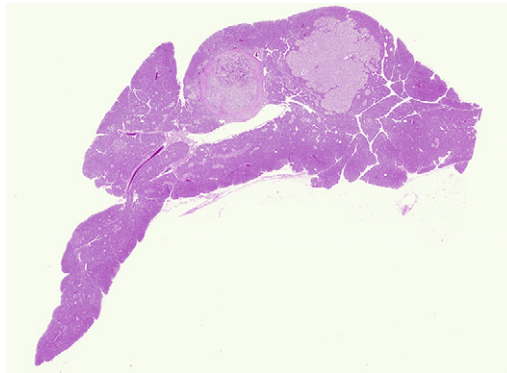

Fig. 1. Subgross view of a pancreatic limb from a ferret with an encapsulated (*left*) and unencapsulated (*right*) pancreatic islet cell tumors, more commonly referred to as insulinomas. These tumors are often found in multiples less than 1 mm in diameter or up to several millimeters in size. (*Courtesy of* Catherine M. Pfent, DVM, College Station, TX.)

the ferret is nonresponsive or exhibiting seizures, owners should drip Karo syrup or honey on the mucous membranes to provide temporary relief from the hypoglycemia until the ferret can be transported to a veterinary facility for supportive care.

If a ferret is comatose or seizuring on presentation, quickly check the blood glucose level for hypoglycemia. If hypoglycemic, place an intravenous catheter for a slow bolus of 50% dextrose (0.25–2 mL) and titrate to effect.[8] Once the seizures have ceased, the patient should be maintained on continuous-rate infusion of fluids supplemented with 5% dextrose. The ferret should be gradually weaned off the dextrose, and maintenance fluids administered during the following 12 to 24 hours. Medications to help maintain their blood glucose levels should also be administered so that clinical signs do not return.

Palliative therapy

Glucocorticoids such as prednisone and prednisolone increase the blood glucose level by increasing hepatic gluconeogenesis, decreasing glucose uptake by peripheral tissues, and inhibiting insulin binding to insulin receptors.[22] Doses of 0.25 to 2 mg/kg by mouth every 12 hours have been used.[8,23] Start at a low dose and increase in small increments as needed to control clinical symptoms and to approach normoglycemia. The blood glucose level should be rechecked within 5 to 7 days to assess if any dose adjustments are needed, and should be rechecked every 2 to 3 months thereafter. Ferrets are relatively resistant to the immunosuppressive effects of prednisolone; however, some ferrets on long-term glucocorticoid therapy may gain weight in the abdominal region and have slow or impaired hair growth in shaved areas.

Diazoxide (Proglycem; Baker Norton), a nondiuretic benzothiadiazide, directly inhibits pancreatic insulin secretion by decreasing the intracellular release of ionized calcium, which subsequently prevents the release of insulin from the insulin granules. In addition, by stimulating the release of epinephrine, diazoxide promotes hepatic gluconeogenesis and glycogenolysis, and decreases the cellular uptake of glucose.[8,22] This medication can be used as the initial palliative therapy in lieu of prednisolone, but is considerably more expensive. Diazoxide can also be used in combination with prednisolone when glucocorticoids alone cannot control clinical symptoms. Recommended dosing starts at 5 to 10 mg/kg by mouth every 12 hours and can be gradually increased to a maximum of 30 mg/kg every 12 hours if lower doses do not control signs adequately.[8,23] Adverse side effects typically include anorexia, vomiting, and diarrhea, but may be abated by administering the medication with food. This medication should be used cautiously in patients with renal disease or congestive heart failure because the conditions can be exacerbated through sodium and fluid retention.[11,22]

Octreotide is a synthetic, long-acting analogue of somatostatin that inhibits the secretion of insulin, glucagon, secretin, gastrin, and motilin. Limited use of this drug has been reported in ferrets, but it may be useful in patients that are not responding to traditional palliative therapy. Reported dosage is 1 to 2 μg/kg every 8–12 hours subcutaneously.[24] Of note, not all insulinomas are responsive to this medication because of the varied expression of somatostatin receptors and the sporadic use of octreotide have produced equivocal results.[8] Moreover, if somatostatin receptors are not present, the administration of octreotide may exacerbate hypoglycemia by suppressing glucagon.[24]

Diet modification

A rapid increase of blood glucose from the ingestion of simple sugars can induce a rebound release of insulin from an insulinoma, thus triggering a hypoglycemic episode.[8,25] Therefore, it is important to instruct owners to discontinue all treats that

are high in simple sugars, including raisins, peanut butter, and any ferret supplements containing corn syrup or other sugar products. A high-protein, low-carbohydrate kibble may be beneficial in decreasing the consumption of simple carbohydrates. Changes should be made gradually to make sure that the ferret is accepting the new diet. Kibble should be available at all times, and multiple feeding stations are recommended so that it is easily accessible. It has been suggested that the development of insulinomas may be prevented by switching to a diet high in protein and fats and low in carbohydrates and fiber.[12] However, studies supporting this theory are currently lacking and further scientific investigations are warranted before specific recommendations can be made.

Definitive treatment of insulinomas

The aforementioned therapeutics only manage the clinical symptoms and do not have any antineoplastic properties. Doxorubicin has been used safely in ferrets as part of chemotherapy protocols for the treatment of lymphoma, and its use for the treatment of insulinomas could be considered.[10] Proposed dosing of doxorubicin for the treatment of insulinomas is 30 mg/m^2 every 3 weeks intravenously, and the cumulative dose should stay below 240 mg/m^2.[14,22] Administration of doxorubicin requires precise venipuncture because inadvertent extravasation can result in severe tissue necrosis. Other reported side effects include bone marrow suppression, gastroenteritis, nephrotoxicity, and cardiac toxicity.[22] Investigational studies in dogs have shown that the chemotherapeutic drugs streptozotocin and alloxan also have direct toxic effects on pancreatic beta cells; however, their use in ferrets has not been evaluated and because of their many toxic side effects, further studies are needed before their use can be recommended.[10,14]

Surgical excision is considered as the treatment of choice for greater clinical resolution and longer survival times. Although an ideal goal would be for patients to be normoglycemic after surgery, some may remain hypoglycemic and many will have recurrence of clinical signs due to tumor metastasis. Case studies have demonstrated that as many as 52% (26 out of 50) of ferrets remained hypoglycemic after surgery, and the reported disease-free intervals have ranged from 0 to 23.5 months.[7,8,26] Because of the likely recurrence of signs, owners should be advised that surgery should not be considered to be curative, but rather may temporarily stop or slow the progression of disease for a longer disease-free interval.

ADRENOCORTICAL NEOPLASIA

In ferrets, the associated syndrome is a type of hyperadrenocorticism and is more commonly known as adrenal disease. Neoplasms of the adrenal cortex have the potential to overproduce one or more of the steroids (glucocorticoids, mineralcorticoids, androgens) that the adrenal gland normally produces. Practitioners should be aware that the clinical disease seen in ferrets is not Cushing disease as seen in dogs when cortisol levels are elevated due to a pituitary tumor. Instead, neoplasms of the adrenal cortex in ferrets usually overproduce one or more of the sex hormones estradiol, androstenedione, or 17α-hydroxyprogesterone.[8,27] Overproduction of the sex hormones (hyperandrogenism) is the most commonly seen disease syndrome, although overproduction of cortisol (hypercortisolism) or aldosterone (hyperaldosteronism) concurrently with the sex hormones has been reported.[28,29] Also in contrast to Cushing disease, the contralateral adrenal gland usually does not atrophy in ferrets with adrenocortical disease.

In a large retrospective study, adrenocortical cell tumors had an incidence of 25% (380 of 1525) of neoplasms identified. In addition to these neoplasms, hyperplasia of

the adrenal cortex was also commonly seen (29%; 439 of 1525) and caused similar clinical signs as adrenocortical neoplasms.[1] The prevalence of lesions may be increasing, as one pathologist has noted some degree of adrenal pathology in 95% of the ferrets necropsied, although not all the ferrets were exhibiting clinical signs at the time of death (Catherine M. Pfent, College Station, TX, personal communication, January 2010). Unilateral disease is noted in approximately 85% of ferrets with adrenocortical disease, whereas the remaining 15% have bilateral disease.[30,31] In cases of unilateral disease the left adrenal gland seems to be more commonly affected, although this may be a factor of the right adrenal gland being more difficult to locate because of its dorsal position over the vena cava. Different histopathologic lesions may be present concurrently in each adrenal gland or within a single adrenal gland. Histopathologic lesions range from hyperplasia to adrenocortical adenoma to adrenocortical carcinomas (**Fig. 2**). Metastasis to other organs is uncommon.[1]

Adrenocortical disease most commonly affects ferrets around 4 years of age and both sexes are represented.[8,30,32] The incidence of adrenal tumors is higher in sterilized ferrets compared with those kept sexually intact, which has led to the theory that the practice of early sterilization may play a role in the development of these tumors.[1,2] This finding is supported by studies where mice that have undergone early-age gonadectomy developed adrenocortical hyperplasia or tumors. Removal of the gonads at a young age removes negative feedback to the hypothalamus, resulting in increased concentrations of gonadotropins. It is theorized that the elevations in gonadotropins in turn persistently stimulate small nests of undifferentiated gonadal cells that may rest under the capsule of the adrenal gland.[8,33] One study showed that regardless of age, gonadectomy in general may predispose ferrets to development of adrenocortical disease. Ferrets in the Netherlands, which are typically castrated or spayed at 1 year of age, seem to develop adrenocortical disease around 3.5 years after sterilization.[34] Another important consideration is that clinical cases in intact ferrets are likely underreported because some of the clinical signs (ie, swollen vulva, aggressive sexual behavior) may be mistaken as normal changes in intact ferrets during the breeding season. Prolonged photoperiods are also thought to play a role in the development of adrenocortical disease. Ferrets kept indoors under artificial lighting are subjected to unnatural prolonged periods of ''daylight'' (>8 hours), which is thought to deplete the body's store of melatonin. As the concentration of this

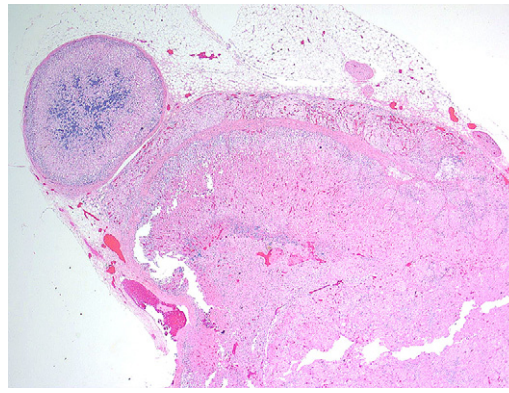

Fig. 2. Low power magnification (2×) of the adrenal gland from a ferret with marked adrenocortical hyperplasia and an extracapsular adenoma. (*Courtesy of* Catherine M. Pfent, DVM, College Station, TX.)

antigonadotropic hormone in blood decreases, there is an increase in gonadotropin-releasing hormone (GnRH) and luteinizing hormone (LH) synthesis and release.[35,36] Finally, a genetic component may also play a role in the development of this disease, especially considering the limited gene pool used in North America resulting in a highly inbred population.[1,4]

Varying degrees of alopecia is the most commonly noted sign, with an incidence of up to 90% in some reports (**Fig. 3**).[8] The hair epilates easily, and the loss is usually symmetric and progressive. Pruritus that may or may not be associated with the alopecia is sometimes noted. Excoriations and erythema may be noted in ferrets with unrelenting pruritus. Vulvar swelling is also commonly noted in more than 70% of the affected female ferrets (**Fig. 4**).[32] Male ferrets may display signs of stranguria due to urethral compression by an enlarged prostate caused by prostatitis or prostatic cysts.[37] Aggressive behavior, which is normal in intact male ferrets during the breeding season, may be observed in sterilized ferrets with adrenocortical disease. Bone marrow toxicity caused by prolonged hyperestrogenism can result in a rare but severe anemia (<15%) with diffuse petechia and ecchymotic lesions in both male and female ferrets. The overproduction of estrogen by the tumor mimics the pancytopenia seen in unbred, intact jills that are in constant estrus.[35]

Diagnostics

Ultrasonographic examination of the adrenal glands allows for evaluation of the size, shape, and structure of each adrenal gland. To look for the left adrenal gland, first obtain a sagittal view of the left kidney. With the cranial pole of the left kidney at the center of the image, angle the transducer gradually from a vertical to horizontal plane to fan the image toward midline until the left adrenal gland is located. The transducer may then need to be slightly rotated to acquire a longitudinal image of the adrenal gland. Images of the right adrenal gland are obtained by scanning the caudal vena cava along the longitudinal plane right where the vessel enters the liver. The right adrenal gland is located dorsal to the caudal vena cava. An alternative technique first scans the liver in a transverse plane to identify the aorta, caudal vena cava, and portal vein. The transducer is then angled in a craniocaudal direction and the caudal vena cava is gradually scanned in a caudal direction until the right adrenal gland is located.[38] Normal adrenal glands can vary greatly in length, but should not vary

Fig. 3. Symmetric hair loss usually starts at the tail and tail base but can progress to the entire body if left untreated.

Fig. 4. Engorged, swollen vulvas are commonly seen in spayed female ferrets with adrenocortical disease. This clinical sign resembles the enlarged vulvas of jills in estrus.

much in thickness. The left adrenal gland on average measures from 5.4 to 9.8 mm in length and ranges 2.3 to 3.6 mm in thickness. The right adrenal gland size ranges from 5.8 to 10.5 mm in length and 2.2 to 3.8 mm in width. Abnormalities can include increased widths of more than 3.9 mm, a rounded appearance, asymmetric poles, increased echogenicity, and mineralization.[38] Color flow Doppler is useful in evaluating the compression of or invasion into the caudal vena cava by the right adrenal gland. Concurrent pathology secondary to adrenocortical disease such as prostatomegaly in male ferrets may also be noted on ultrasonographic examination.

Levels of estradiol, androstenedione, and 17α-hydroxyprogesterone can be measured by a validated sex steroid serum panel available through the Clinical Endocrinology Service at the University of Tennessee (http://www.vet.utk.edu/diagnostic/endocrinology/). These androgens are normally found in minute quantities in neutered ferrets, but may be pathologically elevated in ferrets with adrenocortical disease. A seasonal influence to the hormone cycle has been observed, so that fluctuations in androgen levels may be noted depending on the time of year.[4] A complete blood count should be performed to check for nonregenerative anemia that may be related to an estrogen-induced pancytopenia. Serum biochemistry profiles do not usually have any specific changes, but are important in screening for other common diseases such as insulinoma.

Therapeutics

Most of the medical therapies for hyperadrenocorticism are aimed at controlling the clinical signs through manipulation of hormonal effects. It is important to recognize

that most medications currently in use do not treat the neoplasm, and in many cases the neoplasms continue to grow. The medical options detailed here are good alternatives for most nonsurgical candidates or if there is a recurrence of clinical signs after an adrenalectomy.

Leuprolide acetate (Lupron; Abbott Laboratories) is a long-acting GnRH agonist used for the treatment of prostate and testicular cancer in men and endometriosis in women. When administered at sufficiently high levels for a prolonged period, this GnRH agonist desensitizes GnRH receptors at the pituitary to downregulate the release of gonadotropins follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Current dosing recommendations range from 100 to 200 μg/kg intramuscularly every 4 to 8 weeks and should be tailored by how the ferret is responding to the hormone.[23] Improvement of clinical signs, such as decreased vulvar swelling, decreased pruritus, and decreased aggression is usually noted within 2 weeks. Resolution of dysuria is usually noted within a few days. Hair growth typically occurs within 4 to 8 weeks. The average time to recurrence of clinical signs after administration of one dose of leuprolide acetate (100 μg intramuscularly) is around 3 months (range 1.5–8 months).[39] Most of the controlled studies were performed using the monthly depot form, which should not be confused with the once-a-day injectable or 3- and 4-month depot formulations. The 3- and 4-month formulations anecdotally do not seem to have the expected duration of action, and further clinical studies are recommended.[40] A 1-year leuprolide implant (Viadur; Bayer AG) has been manufactured for the palliative treatment of advanced prostate cancer in humans.[4] However, the amount of leuprolide acetate in this implant (72 mg) is more than 720 times the typical 100-μg dose currently used in ferrets, and toxicologic studies on ferrets should be conducted before the use of the implant can be recommended. Leuprolide acetate is not curative for adrenal neoplasia, and there are conflicting reports on whether or not tumor size is affected. Some of the largest tumors in the author's practice have been in ferrets that have been managed long term (>2 years) with leuprolide acetate. It is thought that some tumors may become autonomous and nonresponsive to the effect of the leuprolide acetate, especially after prolonged therapy.

Deslorelin acetate (Suprelorin; Peptech) is a synthetic analogue of gonadorelin. Deslorelin acetate stimulates LH and FSH secretion that desensitizes the pituitary by downregulating GnRH receptors, which in turn effectively stops the release of gonadotropins. Ferrets receiving a single 3-mg implant had improved clinical signs within 2 weeks, and plasma hormone concentrations remained decreased until recurrence of clinical signs were noted 8.5 to 20.5 months later (mean 13.7 months). Although this hormone is effective in controlling the clinical signs of adrenocortical disease, like Lupron it does not seem to deter tumor growth or metastasis.[41]

Melatonin is low in ferrets exposed to prolonged photoperiods (>8 hours). Oral supplementation of this antigonadotropic hormone at 0.5 mg once a day temporarily improved clinical signs and decreased androgen levels. However, recurrence of clinical signs and elevated androgen levels were noted at an 8-month recheck.[42] Anecdotal oral dosing is recommended at 0.5 to 1.0 mg once a day, 8 to 9 hours after sunrise.[22,23] Melatonin supplements are readily available at most health food stores, but as with any nutraceutical there are no regulations for quality control or false labeling. Melatonin implants are used in the mink and fox pelt industry to promote the development of a thick winter haircoat. In one clinical trial, 5.4-mg implants for mink (Neo Dynamics LLP, Lake Delton, WI, USA) were implanted subcutaneously into ferrets; findings included resolution of vulvar swelling in 1 to 2 weeks and hair growth by 6 to 8 weeks. Lethargy in the first 3 to 5 days after injection was the only side effect noted. The ferrets were only followed for 3 to 4 months, and long-term

studies are needed to determine the duration of efficacy.[36] At present, a 5.4-mg implant (Ferretonin; Melatek LLC, Middleton, WI) is being marketed for ferrets, with good anecdotal results, but studies evaluating the long-term efficacy have not yet been published.[4]

The following drugs have been used anecdotally to help shrink enlarged prostates more quickly while waiting for leuprolide acetate to become effective, but controlled studies have not been conducted on their safety and efficacy in ferrets. Bicalutamide (Casodex; AstraZeneca) and flutamide (Eulexin; Schering-Plough) are androgen receptor blockers used to treat prostate hyperplasia and prostate cancer in men and in ferrets, and have had some anecdotal benefit for severe prostate cases and for aggression in ferrets. Anastrozole (Arimidex; AstraZeneca), a drug used to treat breast cancer in humans, inhibits the synthesis of estradiol and estrogen by inhibiting the catalytic enzyme aromatase. This drug may be useful in ferrets with elevated estradiol levels. Finasteride (Proscar/Propecia; Merck) is an antiandrogen used in men for the treatment of benign prostatic hyperplasia, prostate cancer, and male pattern baldness. It prevents the conversion of testosterone to dihydrotestosterone, and has been used in ferrets in combination with leuprolide acetate without any reported side effects.[4,8,40]

The aforementioned therapies are aimed at controlling the clinical signs through suppression of hormone production, release, or binding to receptor sites, but do not appreciably treat the diseased adrenal tissue. Mitotane (Lysodren; Bristol-Myers Squibb) has been used to chemically debulk the adrenal gland, but has fair to poor efficacy, depending on the type of tumor involved. The chemical debulking is not specific to the zona reticularis, where androgens are produced. This drug can be especially detrimental if the ferret has a concurrent insulinoma, because it decreases the level of circulating cortisol and may precipitate a hypoglycemic episode. Reported dosing consists of 50 mg every 24 hours for a week, followed by maintenance dosing of 50 mg every 48 to 72 hours. Resolution of clinical signs is highly variable, and the clinical signs often recur once the medication is discontinued.[4,8,22,23]

Adrenalectomy of diseased adrenal glands alleviates clinical signs in most ferrets and carries a good long-term prognosis. In one study the 1- and 2-year survival rates were 98% and 88%, respectively. The same study also found that the survival time was not significantly affected by the type of tumor involved or if unilateral or bilateral disease was present.[43] Although surgical resection of diseased adrenal gland is the treatment of choice for many practitioners, recurrence of disease after adrenalectomy is possible.[44] Various surgical techniques for the removal of adrenal glands have been reviewed thoroughly in the literature.

Management of Conditions Secondary to Adrenocortical Disease

Male ferrets with adrenocortical disease may present on emergency for urinary obstruction secondary to prostatomegaly. Urethral catheterization with a 3.5F red rubber catheter, tomcat catheter, or ''slippery sam'' catheter is indicated for relief of the obstruction (**Fig. 5**). Under sedation, the penis is exposed from the prepuce by placing gentle but cranially directed pressure at the base of the os penis. Once exposed, gauze can be hooked at the curved end of the os penis to keep the penis exposed. The opening to the urethra can be located just lateral to the tip of the penis. Leuprolide acetate should be administered immediately to help decrease the size of the prostate within a few days. Multiple antiandrogens have been anecdotally used to treat prostatic enlargement, but controlled studies have not been conducted to confirm if the antiandrogens have any additional benefit in comparison with giving leuprolide acetate alone. Any effects from postrenal azotemia should also be immediately

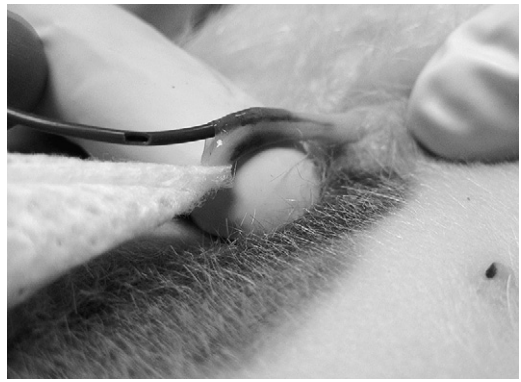

Fig. 5. Male ferrets with prostatomegaly are at risk of obstruction of their urinary tract. Urinary catheterization can be performed in cases of urinary tract obstruction. Gauze can be hooked at the curved end of the os penis to keep the penis exposed. The opening of the urethra is just lateral to the tip of the exposed penis.

addressed. Placement of a temporary tube cystostomy has been described in cases when the maintenance of a urethral catheter had failed.[45]

Pancytopenia secondary to hyperestrogenism is a rare life-threatening condition that requires intensive supportive care. Affected ferrets are severely anemic (<15%), and may have petechia or ecchymotic lesions caused by thrombocytopenia. In the author's practice, ferrets presenting with these clinical signs have failed to respond to leuprolide acetate. If surgical excision of the estrogen-producing tumor is to be attempted, multiple transfusions may be required preoperatively, perioperatively, and postoperatively. Hospitalization for intravenous fluids, blood transfusions, and supportive care is often required until the bone marrow can regenerate after the source of excess estrogen production has been removed. Owners should be advised that these ferrets have a poor prognosis, especially in cases where the adrenal neoplasm is nonresectable.

SUMMARY

At present, insulinomas and adrenocortical disease are the 2 most commonly seen neoplasms that affect middle-aged and older ferrets. A thorough understanding of the diagnostics and treatment options of both these diseases is important to appropriately manage their medical conditions. Although surgical excision is still a good treatment option for most ferrets with insulinomas and adrenocortical neoplasia, appropriate medical management can provide a good quality of life for ferrets when surgery is not an option.

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